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# The Development of $L_2X_2Ru{=}CHR$ Olefin Metathesis Catalysts: An Organometallic Success Story

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**ABSTRACT**
In recent years, the olefin metathesis reaction has attracted widespread attention as a versatile carbon−carbon bond-forming method. Many new applications have become possible because of major advances in catalyst design. State-of-the-art ruthenium catalysts are not only highly active but also compatible with most functional groups and easy to use. This Account traces the ideas and discoveries that were instrumental in the development of these catalysts, with particular emphasis on $(PCy_3)_2Cl_2Ru{=}CHPh$ and its derivatives. The discussion includes an analysis of trends in catalyst activity, a description of catalysts coordinated with *N*-heterocyclic carbene ligands, and an overview of ongoing work to improve the activity, stability, and selectivity of this family of $L_2X_2Ru{=}CHR$ complexes.

The very foundation of organic synthesis consists of reactions that can reliably and efficiently form carbon−carbon bonds. One of these reactions, olefin metathesis, is currently undergoing an exciting renaissance as a synthetic method. Although double-bond scrambling reactions were initially reported in the mid-1950s,[1] it was not until several years later that Calderon and co-workers recognized that both ring-opening polymerization and the disproportionation of acyclic olefins were the same reaction. They coined the term "olefin metathesis" in 1967,[2] which we currently understand to mean the metal-catalyzed redistribution of carbon−carbon double bonds. As shown in Figure 1, this transformation has a variety of applications. The illustrated examples include ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMET), ring-opening metathesis (ROM), and cross-metathesis (CM or XMET). Through these reactions, olefin metathesis provides a route to unsaturated molecules that are often challenging or impossible to prepare by any other means. Some of the most impressive achievements include the use of ROMP to make functionalized polymers, the syntheses of small to large heterocyclic systems by RCM, and the CM of olefins with pendant functional groups.

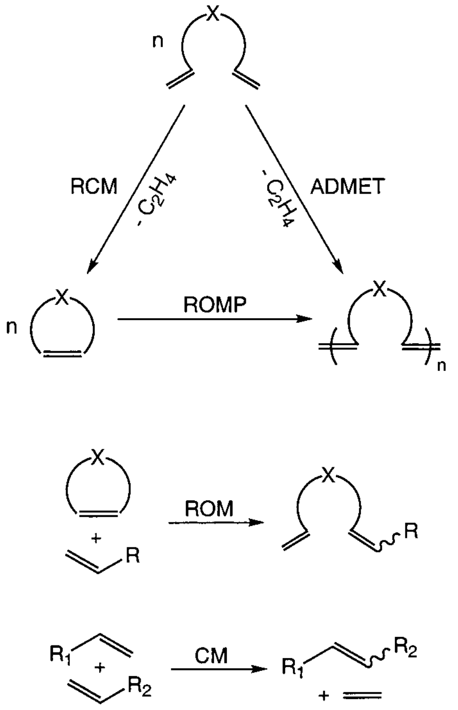

**FIGURE 1.** A variety of olefin metathesis reactions.

A number of reviews have been published in this area, all of which focus on the ever increasing uses of olefin metathesis in organic synthesis and polymer chemistry.[3,4] Until a few years ago, however, the scope of the reaction was quite limited because of insufficient catalyst performance. It is only through major advances in catalyst design that tremendously expanded applications have recently become possible. To a large extent, these efforts to improve catalyst performance have been motivated and inspired by the desire to apply olefin metathesis to new synthetic challenges. For these reasons, the focus of this Account is the interplay between catalyst development and applications that has characterized progress in the field.

The organization of the Account follows the chronology in Figure 2. Our aim throughout is to highlight the strengths and weaknesses of various catalyst systems, and especially emphasize the improvements that were made at each stage of development. In this way, we intend to trace the evolution of ruthenium-based olefin metathesis catalysts from simple salts of limited utility to single-component, homogeneous catalysts that combine excellent activity with broad functional group tolerance.

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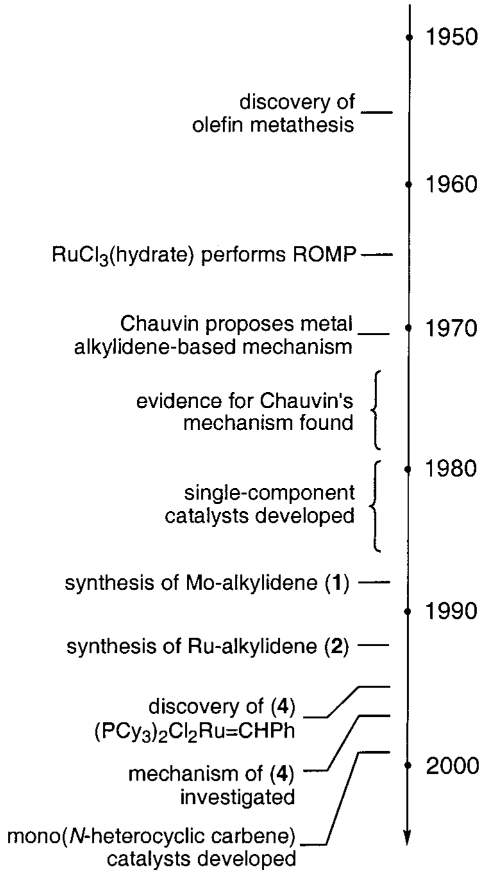


**FIGURE 2.** Time line of milestones in the development of olefin metathesis catalysts.

## Background

From the mid-1950s to the early 1980s, all olefin metathesis was accomplished with poorly defined, multicomponent homogeneous and heterogeneous catalyst systems. These systems consisted of transition metal salts combined with main group alkylating agents or deposited on solid supports. Some of the classic combinations include $WCl_6/Bu_4Sn$, $WOCl_4/EtAlCl_2$, $MoO_3/SiO_2$, and $Re_2O_7/Al_2O_3$, among many others. Due to their low cost and simple preparation, these systems have an important place in commercial applications of olefin metathesis like the Shell Higher Olefin Process and the neohexene process.[4b]

The utility of these catalysts, however, was limited by the harsh conditions and strong Lewis acids that they required and that made them incompatible with most functional groups. In addition, the reactions were difficult to initiate and control because very little of the active species formed in the catalyst mixtures. These problems motivated extensive work to better understand olefin metathesis, including detailed mechanistic studies. Many schemes were proposed over the years, but ultimately, the scheme developed by Chauvin was found to be most consistent with the experimental evidence, and it remains the generally accepted mechanism today.[5,6] As illustrated in Figure 3, Chauvin proposed that olefin metathesis involves the interconversion of an olefin and a metal alkylidene. This process is believed to occur via a metallacyclobutane intermediate by alternating [2 + 2] cycloadditions and cycloreversions.

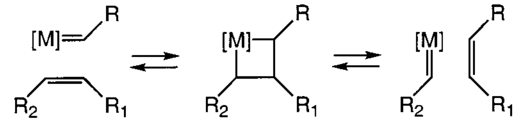


**FIGURE 3.** Mechanism of olefin metathesis.

This mechanism influenced work on catalyst development in that it provided both a design rationale and a way to begin to understand catalyst activity. Subsequent efforts to synthesize alkylidene and metallacyclobutane complexes led to the discovery of the first single-component homogeneous catalysts for olefin metathesis during the late 1970s and early 1980s. These new catalysts included $(CO)_5W{=}CPh_2$,[7] bis(cyclopentadienyl) titanocyclobutanes,[8] tris(aryloxide) tantalacyclobutanes,[9] and various dihaloalkoxide-alkylidene complexes of tungsten.[10] As well-defined complexes, these catalysts exhibited better initiation and higher activity under milder conditions than ever before, and they enabled researchers to study structure–activity relationships and mechanism in detail.

The molybdenum and tungsten alkylidenes of the general formula $(NAr)(OR')_2M{=}CHR$ were the first of these catalysts to become widely used, particularly the molybdenum complex (**1**), where Ar = $2,6\text{-}Pr^i_2\text{-}C_6H_3$, R = $CMe_2Ph$, and R′ = $C(CH_3)(CF_3)_2$.[11,12] The most impressive feature of **1** is its high activity, which allows it to react with both terminal and internal olefins and to ROMP low-strain monomers, as well as to ring-close sterically demanding and electron-poor substrates.[11−13] However, this catalyst and others based on the early transition metals are limited by the high oxophilicity of the metal centers, which renders them extremely sensitive to oxygen and moisture. As an example, the synthesis and handling of **1** requires an inert atmosphere and rigorously purified, dried, and degassed solvents and reagents. Aside from these inconveniences, early metal catalysts are more fundamentally limited by moderate to poor functional group tolerance, which reduces the number of potential substrates. Complex **1**, for instance, is incompatible with aldehydes and alcohols.[14] Of course, this problem of functional group tolerance may be evaded with protecting group strategies, but these are often tedious.

This brief history of olefin metathesis provides a context for subsequent work. The development of single-component catalysts was a major advance, but a great deal of room for improvement remained. Continuing research was motivated by the prospect of solving the problems related to oxophilicity and functional group tolerance, thereby unlocking even more of the potential of this reaction.

## Functional Group Tolerance: Why Ruthenium?

In any catalyst system, functional groups in the substrate or solvent (including oxygen and water) can interfere with catalytic activity in several ways. They may bind competitively to the active metal center and deactivate the catalyst, or they may react directly with the metal center and

| Titanium | Tungsten | Molybdenum | Ruthenium |
|---|---|---|---|
| Acids | Acids | Acids | **Olefins** |
| Alcohols, Water | Alcohols, Water | Alcohols, Water | Acids |
| Aldehydes | Aldehydes | Aldehydes | Alcohols, Water |
| Ketones | Ketones | **Olefins** | Aldehydes |
| Esters, Amides | **Olefins** | Ketones | Ketones |
| **Olefins** | Esters, Amides | Esters, Amides | Esters, Amides |

↑ Increasing Reactivity

**FIGURE 4.** Functional group tolerance of early and late transition metal olefin metathesis catalysts.

destroy the active species. Thus, the key to improved functional group tolerance in olefin metathesis is the development of a catalyst that reacts preferentially with olefins in the presence of heteroatomic functionalities.

The advent of single-component catalysts allowed the relationships between structure and reactivity to be more clearly defined. These catalysts were observed to react more selectively with olefins as the metal centers were varied from left to right and bottom to top on the periodic table.[15] This trend is illustrated for titanium, tungsten, molybdenum, and ruthenium in Figure 4.

Farthest to the left, titanium and tungsten catalysts are most strongly disposed to olefinate ketones and esters; in fact, this transformation is useful in organic synthesis.[16] In comparison, molybdenum catalysts are more reactive toward olefins, although they also react with aldehydes and other polar or protic groups. Farthest to the right, ruthenium reacts preferentially with carbon−carbon double bonds over most other species, which makes these catalysts unusually stable toward alcohols, amides, aldehydes, and carboxylic acids. Because of this trend, it is possible to increase the functional group tolerance of an olefin metathesis catalyst by focusing on a later transition metal, such as ruthenium.

## From $RuCl_3$(hydrate) to Well-Defined Ruthenium Alkylidene Complexes

In retrospect, ruthenium was an excellent candidate, but it was not seriously considered for more than two decades of research. At the time, this situation was caused by the discouragingly low metathesis activity of ruthenium salts, as well as a limited understanding of how to achieve functional group tolerance. Several reports from the 1960s had, in fact, described the ROMP of norbornene derivatives with $RuCl_3$(hydrate) in refluxing ethanol and under aqueous emulsion conditions.[17] The polymer yields were small, but the observation that ROMP could take place in these protic solvents at all was an important precedent.

Starting in the late 1980s, the potential of ruthenium catalysts for ROMP applications was reexamined. In fact, $RuCl_3$(hydrate) did indeed catalyze ROMP, but the polymerizations were preceded by long initiation periods (20 h or more) when performed in organic solvents.[18,19] In an attempt to decrease the initiation times, the reactions were repeated under more strictly anhydrous conditions, but this change caused initiation to take even longer. Quite unexpectedly, however, ROMP initiated after only 30 min in aqueous solution. Thus, water was found to be not only compatible with this catalyst system but actually beneficial to the initiation process.

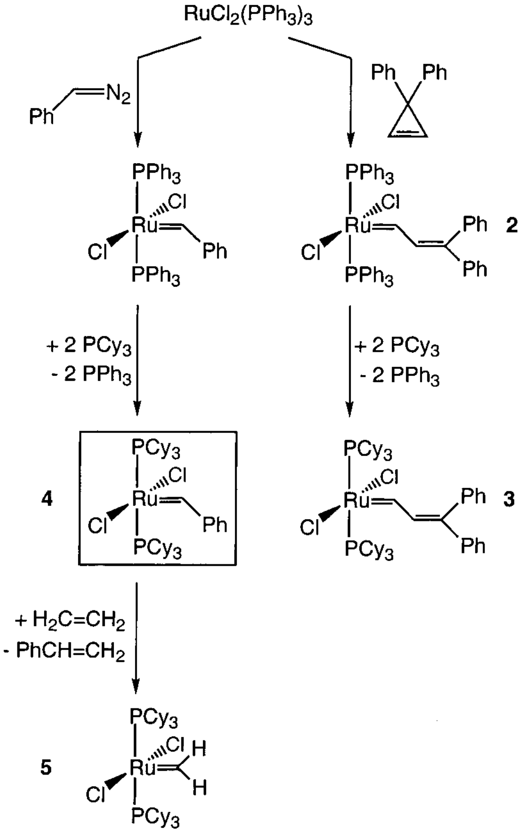
Upon screening of other simple ruthenium complexes, $Ru(H_2O)_6(tos)_2$ (tos = *p*-toluenesulfonate) was found to have even shorter initiation times, on the order of a few minutes.[20] This catalyst was able to ROMP functionalized norbornene, 7-oxanorbornene, and norbornadiene monomers, including hydroxyl-, carboxyl-, alkoxy-, and carboximide-substituted derivatives. The polymers from these reactions were obtained consistently in greater yields, and with higher molecular weights and lower polydispersities, than those prepared with most other catalysts known at that time. Furthermore, the $RuCl_3$(hydrate) and $Ru(H_2O)_6$-$(tos)_2$ catalyst solutions, which contained ruthenium−olefin adducts observable by $^1H$ NMR, could be recycled a number of times.[21]

The initiation process remained unclear, but a number of observations suggested that the active species was a ruthenium alkylidene. For instance, acyclic olefins added during ROMP became incorporated at the ends of the polymer chains.[22] A detailed analysis of the polymer microstructure and the trends in olefin activity were consistent with a chain-transfer mechanism, which had been seen previously with other alkylidene catalysts. Although none of the ruthenium alkylidene complexes known at that time could perform olefin metathesis, the success of early metal alkylidene catalysts was very suggestive. Thus, early attempts to generate ruthenium alkylidene species included the addition of ethyl diazoacetate, a carbene source, to ruthenium precursors. This reaction with $Ru(H_2O)_6(tos)_2$ produced a species with activity higher than that of $Ru(H_2O)_6(tos)_2$ alone.[23] In fact, this solution could even initiate the ROMP of monomers less strained than norbornene, such as cyclooctene, whereas the activity of $RuCl_3$(hydrate) or $Ru(H_2O)_6(tos)_2$ is limited to more highly strained substrates.

A breakthrough occurred when the methodology for the synthesis of tungsten alkylidenes, in which 3,3-disubstituted cyclopropenes are used as carbene precursors, was applied to the synthesis of a ruthenium catalyst.[24] The addition of diphenylcyclopropene to $RuCl_2(PPh_3)_3$ led to the isolation of **2** [as a mixture of *cis*- and *trans*-bis(phosphine) isomers], the first well-defined, metathesis-active ruthenium alkylidene complex (Scheme 1).[25]

Catalyst **2** polymerizes norbornene effectively in the presence or absence of water or ethanol. More significantly, a propagating alkylidene species is observed by $^1H$ NMR during the ROMP of norbornene. As indicated in

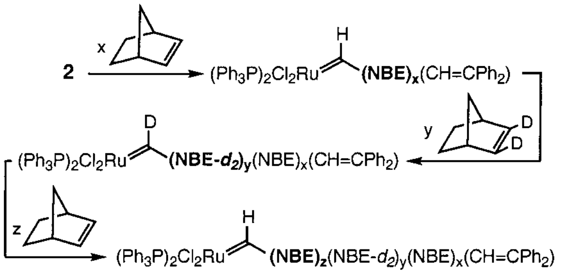
**Scheme 1**



Scheme 2, the propagating alkylidene signal vanishes when 2,3-dideuterio-norbornene is added, but reappears when protio-norbornene is added once again. This sequence of norbornene additions results in a block copolymer with alternating protio and deuterio segments. Additional experiments show that chain termination and transfer are slow relative to propagation, which also suggests a living polymerization.[26]

Although the initiation behavior and functional group tolerance of **2** were exciting, its activity was limited to the ROMP of highly strained monomers. To extend this activity to the ROMP of low-strain monomers and the metathesis of acyclic olefins, the ligand environment was modified in a systematic way. Based on the trend followed by early transition metal catalysts, for which metathesis activity increases with more electron-withdrawing ligands,[12] a variety of cationic complexes and derivatives containing less basic phosphines were prepared and tested. After months of exploring this strategy without success, the most basic phosphine in the stockroom, which happened to be $PCy_3$ (Cy = cyclohexyl), was used instead and led to[27] a fortuitous discovery—the larger and more basic the phosphine, the higher the metathesis activity.

**Scheme 2**



As illustrated in Scheme 1, the $PCy_3$ analogue (**3**) and other derivatives can be obtained by phosphine exchange.[28] The catalytic activity of these complexes increases with the basicity of the phosphines in the order $PPh_3 \ll PPr^{i}_3 < PCy_3$. The $PCy_3$ derivative **3** catalyzes the ROMP of lower strain monomers, such as cyclopentene, and it became the first ruthenium alkylidene complex active toward acyclic olefins.

Although **3** is not as active as early metal catalysts such as **1**, it is much more versatile due to its functional group tolerance. For example, even in the presence of the common protecting groups trifluoroacetyl and *tert*-butoxycarbonyl, **3** is able to cyclize $\alpha,\omega$-dienes to five-, six-, and seven-membered carbo- and heterocycles in good yields.[29] This robust catalyst is air-stable as a solid and retains its activity even when exposed to water, alcohols, or acids. These characteristics make catalyst **3** ideal for a wide range of synthetic organic applications.

The difficulty of synthesizing diphenylcyclopropene initially limited the availability of these complexes, but the alternate reaction of $RuCl_2(PPh_3)_3$ with alkyl- and aryldiazoalkane compounds led to good yields of substituted akylidenes (Scheme 1).[30] With a variety of complexes in hand, the fundamental reactions of ruthenium alkylidenes were examined. The benzylidene catalyst **4**, for example, undergoes metathesis with ethylene within minutes at room temperature to quantitatively form the methylidene derivative **5**. This complex was the first metathesis-active methylidene species ever isolated. In contrast, the diphenylvinyl derivative **3** reacts slowly with ethylene, even under forcing conditions, and only partially converts to the methylidene (20% after a few hours). This difference in initiation properties is also reflected in the molecular weight distributions of ROMP products, which is broader for **3** than for **4**.[30a] The most active catalyst of this series, complex **4**, combines the bulky and strongly electron-donating $PCy_3$ ligands with the readily initiated benzylidene moiety.

## The Applications of Ruthenium-Based Catalysts

These first members of an entire family of $L_2X_2Ru{=}CHR$ complexes opened new vistas in olefin metathesis. Because these catalysts possess a favorable combination of activity and functional group compatibility, they attracted a great deal of attention soon after the initial reports. In 1990, for example, only 35 publications regarding olefin metathesis were published.[31] Slightly less than a decade later, in 1999, the number of publications rose to 250 during this year alone. Of this literature, 75% of the authors described using ruthenium-based catalysts for olefin metathesis, and a full 62% specifically used complex **3** or **4**. Because many reviews have focused on applications,[3] we present here only a brief survey of reports that have been connected with catalyst development in this

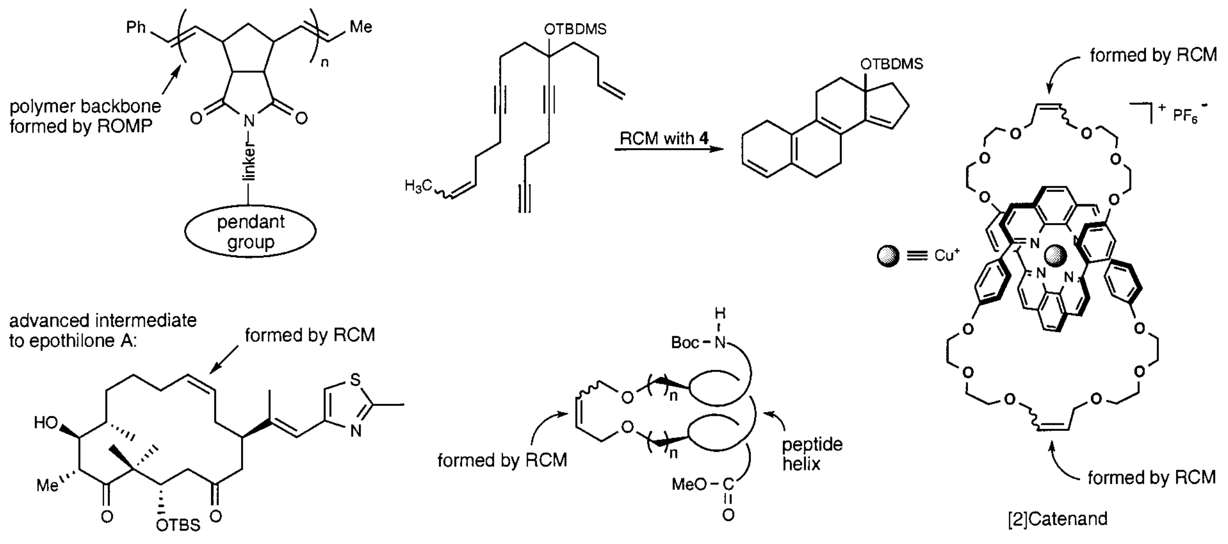


**FIGURE 5.** Applications using $(PCy_3)_2Cl_2Ru{=}CHPh$ (**4**).

laboratory. A selection of these applications is illustrated in Figure 5.

Historically, the most common application of olefin metathesis has been the preparation of new materials through ROMP. ROMP is a convenient route to polymers because it maintains backbone unsaturation and allows the direct incorporation of functionality from the monomer. The functional group tolerance of ruthenium catalysts has extended ROMP to a more diverse set of monomers. In a recent example, **4** was used to synthesize side-chain liquid crystalline polymers from mesogen-containing monomers.[32] Others have applied ROMP to highly functionalized and hydrophilic substrates, such as norbornene derivatives with pendant sugars, amino acids, and vancomycin subunits (Figure 5).[33] The living nature of ROMP catalyzed by **3** and **4** leads to nearly monodisperse polymers and allows the lengths of polymer chains to be controlled by chain termination or adjustment of the monomer/catalyst ratio. Because the propagating species remains attached at the end of the polymer chain even after complete consumption of the monomer, it is also possible to synthesize block copolymers by this route.[32b] Oligomers and polymers may also be synthesized with ADMET chemistry.[3d] For example, main-chain ferroelectric liquid crystal oligomers have been made by the ADMET of $\alpha,\omega$-diene mesogens with catalyst **3**.[34]

The scope of olefin metathesis has been further extended in aqueous media through modifications of catalyst **4**. Although **4** is active in the presence of protic species, it is limited by being insoluble in water, and emulsion conditions are not suitable for all applications.[35] Substitution of the $PCy_3$ ligands with water-soluble phosphines, such as $Cy_2P(CH_2)_2NMe_3{}^+Cl^-$ and $Cy_2P[4\text{-}(N,N\text{-dimethylpiperidinium})]^+Cl^-$, makes these complexes water soluble. As an example of their activity, these catalysts promote the living ROMP of water-soluble monomers in the presence of Brönsted acids (e.g., HCl).[36] The acid serves to protonate a phosphine ligand and also remove hydroxide ions that lead to catalyst decomposition. These water-soluble catalysts also allowed the RCM reaction in water and methanol for the first time.[37] It is necessary to use phenyl-substituted substrates for these reactions instead of $\alpha,\omega$-dienes because the propagating methylidene species is unstable.

Without question, the area of olefin metathesis that has expanded most dramatically in recent years is RCM. Catalysts **3** and **4** have made it possible to cyclize substrates containing diverse functionality.[3] New methodologies, such as ring-opening/ring-closing sequences[38] and the RCM of dienynes (Figure 5),[39] have allowed the construction of fused ring systems[40] and bridged bicycloalkenes.[41] RCM is proving useful in total synthesis, where it has been applied to targets ranging from relatively small molecules such as frontalin[42] to complex ones such as epothilone A (Figure 5).[43] It is also possible to use this methodology to cyclize polypeptides and introduce carbon–carbon cross links into peptides (Figure 5).[44]

One of the major applications of RCM has been the synthesis of medium to large ring systems. This methodology was first utilized in the synthesis of macrolides by Villemin and Tsuji.[45] Most importantly, these early workers demonstrated that it was essential to work at substrate concentrations of $\leq 6 \times 10^{-3}$ M to obtain cyclic products rather than oligomers. Subsequent work in this area with catalysts **1** and **4** has included the synthesis of manzamin A and other macrolides.[46]

Several RCM applications take advantage of templates to direct ring formation. An example of this strategy is the ring closing of polyether-containing olefins, which can be assisted by preorganization around alkali metal ions.[47] Similarly, phenanthroline-containing olefins assembled with $Cu^+$ templates undergo RCM to form [2]catenates in excellent yields (Figure 5).[48]

There has also been renewed interest in CM applications. For instance, the CM of unhindered terminal olefins with symmetrically disubstituted internal olefins provides the desired cross products in good to excellent yields.[49] This methodology was successfully extended to several terminal olefins with allylic disubstitution, such as acrolein acetals and vinyl boronates.[49b,50]

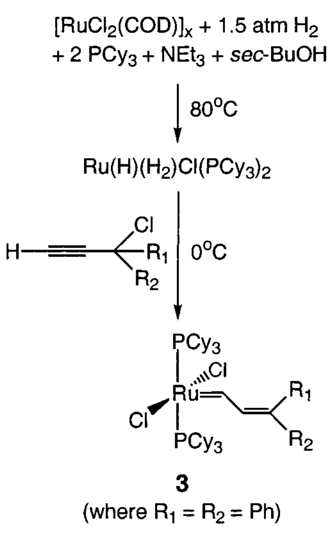
Although most of these applications have been developed in academic laboratories, olefin metathesis with ruthenium-based catalysts has several attractive features from an industrial perspective. Because the catalysts are quite active, the metal species is present in small amounts. Catalyst loadings for the ROMP of highly strained monomers with **4** can be as low as 0.01 mol % (monomer: catalyst = 10 000). A typical catalyst loading for RCM reactions with **4** is 5 mol %. For RCM applications, we have shown that this residual ruthenium can be removed from the products by extraction with tris(hydroxymethyl)-phosphine.[51] Furthermore, these catalysts operate under mild conditions and generate only volatile side products during RCM and CM, typically ethylene. For these reasons, ruthenium-based olefin metathesis catalysts are currently being applied to the synthesis of pheromones and other specialty chemicals.

## Improvements in Catalyst Synthesis

As the use of ruthenium-based catalysts expanded and large-scale applications of olefin metathesis became worthwhile, the demand for these catalysts also increased. However, the diazo route shown in Scheme 1 is not ideal because it uses unstable reagents, requires large amounts of solvent, and involves an extra substitution step to make the more active $PCy_3$ derivative. To meet the need for a better synthesis, a convenient one-pot procedure was developed on the basis of the insertion of alkynes into ruthenium−hydride bonds. As outlined in Scheme 3, the hydrido chloride complex $Ru(H)(H_2)Cl(PCy_3)_2$, generated in situ, reacts rapidly with propargyl chlorides to give the desired alkylidene complex (**3**).[52,53] Although a variety of routes to members of this catalyst family have been developed, the synthesis in Scheme 3 is the method of choice because it begins with readily available starting materials and proceeds in high yields (~95% with tertiary propargyl chlorides). This preparation is routinely carried out on a 10-kg scale in commercial laboratories.

Catalysts **3**, **4**, and the $PCp_3$ (Cp = cyclopentyl) analogue of **4** are currently available from a number of suppliers.[54] The $PCp_3$ and dimethylvinyl carbene derivatives are less active than the $PCy_3$-benzylidene catalyst (**4**), but they are less expensive and often sufficient for ROMP applications. The widespread use of these catalysts has been facilitated, no doubt, by their convenient synthesis, commercial availability, and decreasing cost.

**Scheme 3**



**3**
(where $R_1 = R_2 = Ph$)

## Mechanistic Studies

Work to better understand the mechanism of these catalysts began soon after their discovery. Numerous crystal structures show that $L_2X_2Ru{=}CHR$ complexes are arranged in a distorted square pyramidal geometry with the alkylidene in the axial position and the trans phosphines and halides in the equatorial plane.[30] We have proposed a mechanism based on extensive kinetic studies that is consistent with the observed activity trends.[55] As illustrated in Figure 6, the first step involves olefin coordination to the metal center, presumably cis to the alkylidene. In one possible pathway (A), phosphine dissociation and alkylidene rotation occur in order to generate the 16-electron intermediate **6**, in which the olefin remains cis to the alkylidene. This intermediate then undergoes metallocyclobutane formation cis to the bound phosphine, followed by cleavage to release the metathesis products. Although phosphine dissociation is not an obvious part of the mechanism, it is supported by (1) kinetic data,[55] (2) the observation of chelated mono-(phosphine) intermediates during the ROMP of 3-functionalized cyclobutenes,[56] (3) the reactivity patterns of imidazoles with $L_2X_2Ru{=}CHR$ complexes,[57] (4) the isolation of a ruthenium catalyst "caught in the act", in which an intramolecularly coordinated olefin has displaced one of the phosphines,[58] (5) the observation of mono(phosphine) intermediates by electrospray ionization tandem mass spectrometry,[59] and (6) quantum molecular dynamics studies.[60]

An alternate pathway (B) involves phosphine dissociation and rearrangement of the olefin trans to the remaining phosphine. This intermediate (**7**) then undergoes metallocyclobutane formation trans to the phosphine. Although pathway B was initially disfavored because of reversibility considerations, it is currently being reconsidered in more detail. The mechanism where both phosphines remain bound to the metal center appears to make an insignificant contribution to the overall activity.[55]

The activity of $(PCy_3)_2Cl_2Ru{=}CHPh$ (**4**) is highly dependent on the identity of the X- and L-type ligands. Whereas catalyst activity increases with larger and more electron-donating phosphines, it decreases with larger and more electron-donating halides. These trends can be rationalized with the proposed mechanism. One of the contributions of the phosphine ligands is $\sigma$-donation to the metal center, which promotes formation of the mono-(phosphine) olefin complex by facilitating phosphine dissociation and stabilizing the vacant trans site in **6**.[55,61] Perhaps even more importantly, $\sigma$-donation helps stabilize the 14-electron metallacyclobutane intermediate. In these ways, catalyst activity is directly related to the electron-

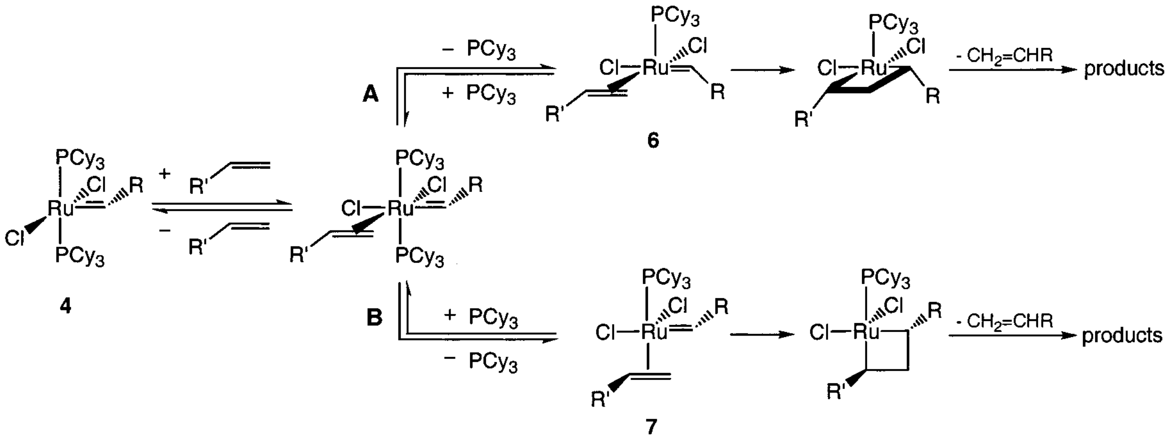


**FIGURE 6.** Proposed mechanism for $(PCy_3)_2Cl_2Ru{=}CHPh$ (**4**).

donating ability of the phosphine ligands. The steric bulk of the ligands may also contribute to phosphine dissociation by destabilizing the crowded bis(phosphine) olefin complex. In hindsight, then, the choice of $PCy_3$ was a fortunate circumstance, because those phosphines that are more basic or bulkier than $PCy_3$ result in unstable complexes.

In contrast to the trend for phosphines, the halide ligands correlate with decreasing activity as they become larger and more strongly electron donating, in the order $Cl > Br \gg I$. Since the incoming olefin may initially bind trans to a halide, a more electron-donating halide should weaken the ruthenium−olefin bond and disfavor olefin coordination. These small changes in the steric and electronic character of the X- and L-type ligands combine to influence olefin binding, phosphine dissociation, and the stability of intermediates, which results in large variations of catalyst activity.

The overall activity also depends on catalyst initiation and thus on the nature of the alkylidene moiety. In general, alkyl-substituted alkylidenes display more efficient initiation than the methylidene complex (**5**).[62] The initiation of ester-subsituted alkylidenes $[Ru]{=}CHCO_2R$ occurs even more rapidly than for alkyl derivatives, but these complexes also tend to be less stable.[63] The benzylidene (**4**) seems to be an intermediate case; the phenyl group is somewhat electron withdrawing, but its size may assist phosphine dissociation.

The catalyst lifetime is another important factor in its overall activity. The kinetics of the thermal decomposition pathways of various catalysts reveal that substituted alkylidene complexes decompose by a different mechanism than the methylidene complex, which is the only propagating species observed during RCM. For substituted alkylidenes, observations are consistent with a bimolecular decomposition mechanism involving phosphine dissociation followed by coupling of mono(phosphine) species.[64] In contrast, the methylidene complex decomposes through a unimolecular pathway that is independent of concentration. In this way, the relative stabilities of the initiating and propagating species directly influence catalyst activity. These observations also explain why relatively high catalyst loadings are required for RCM reactions.

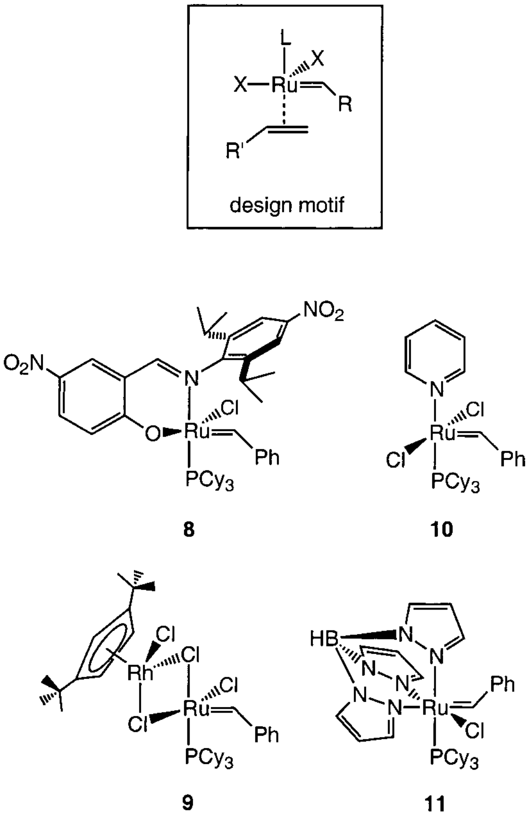
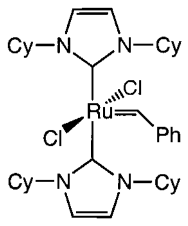


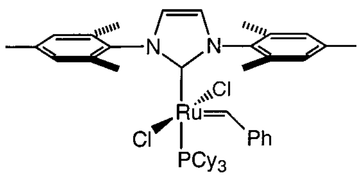
**FIGURE 7.** Applications of the catalyst design motif to $L_2X_2Ru{=}CHR$ complexes.

## Recent Developments in Catalyst Design

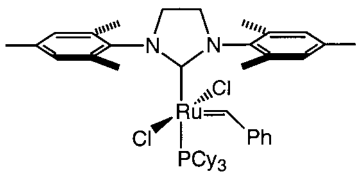
These mechanistic studies allowed us to identify a number of factors that contribute to the activity of these catalysts. The key insight was that $(PCy_3)_2Cl_2Ru{=}CHPh$ forms a highly active mono(phosphine) intermediate during the catalytic cycle. As a design motif, this intermediate became a starting point for the development of improved catalysts. The examples in Figure 7 show a variety of ligand arrays that incorporate this design motif. Although all of these complexes are active to some degree, they tend to have either enhanced stability and low activity, or the reverse, high activity and poor stability. The bidentate salicylaldimine complex (**8**) is an example of the first case; it is significantly more stable than the parent complex **4** at



**12**



**13**



**14**

**FIGURE 8.** Ruthenium catalysts containing *N*-heterocyclic carbene ligands.

elevated temperatures, but its activity is much lower.[65] In contrast, the heterobimetallic (**9**) and pyridine-coordinated (**10**) complexes have very high activity for only a short time before the catalysts decompose.[66] The tris(pyrazolyl)borate catalyst (**11**) has similar problems; acid must be added for initiation, but even then its activity is poor.[67]

The properties of these complexes illustrate several mechanistic points. First, for olefin metathesis to begin, at least one of the ancillary ligands must be labile enough for catalyst activation. Complexes **8** and **11** do not readily meet this condition, and their activity is limited. Second, because decomposition of **4** is known to be second order and inversely proportional to phosphine concentration, it is generally important to maintain a low concentration of the mono(phosphine) species. Complexes **9** and **10** do not fulfill this requirement because they contain ancillary ligands that either are too labile or cannot sufficiently stabilize the reaction intermediates. These examples demonstrate that any approach to increase the concentration of the mono(phosphine) intermediate is futile if it also accelerates catalyst decomposition. For this reason, additives such as CuCl and HCl that increase phosphine dissociation enhance catalyst activity but simultaneously promote catalyst decomposition.

Mindful of these lessons, we became interested in the potential of *N*-heterocyclic carbene ligands to meet the necessary criteria.[68] We were prompted to examine these ligands by the report of complex **12** by Herrmann and coworkers (Figure 8).[69] This bis(substituted) complex showed little improvement in activity compared to **4**, but we believed that we could apply the design motif in Figure 7 to this system by making *monosubstituted* derivatives. It

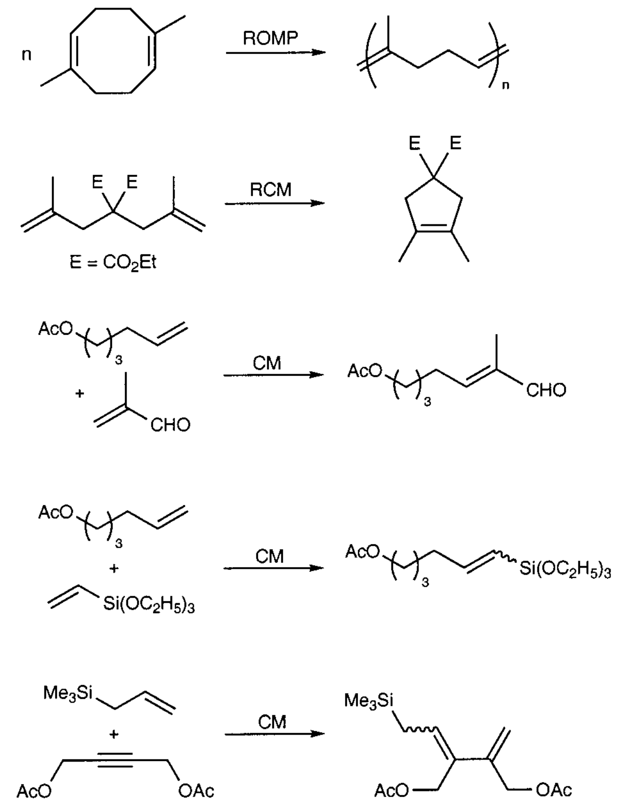


**FIGURE 9.** Applications using catalyst **14**.

is well known that, compared to phosphines, *N*-heterocyclic carbene ligands are stronger $\sigma$ donors and much less labile.[68,70] As a result, the *N*-heterocyclic carbenes in **12** are not able to readily dissociate. A mixed-ligand complex, however, could overcome this problem in two ways. Initially, the more strongly electron-donating carbene ligand might enhance the dissociation of the more labile trans phosphine from the metal center. Then, by virtue of its steric bulk and electron-donating properties, the same ligand should more effectively stabilize the electron-deficient intermediates and promote olefin metathesis.

After exploring a variety of ligand derivatives, we found that a mesityl-substituted *N*-heterocyclic carbene worked well. Our initial disclosure of catalyst **13** (Figure 8)[71] was closely followed by related reports.[72] Soon thereafter, we discovered that catalyst **14**, which contains an *N*-heterocyclic carbene with a saturated backbone, is even more active.[73] These new catalysts display performance that was previously possible only with the most active early metal systems. The superior activity of **14** includes high rates of ROMP for low-strain substrates and even the ROMP of sterically hindered substrates containing trisubstituted olefins such as 1,5-dimethyl-1,5-cyclooctadiene (Figure 9).[74] Both **13** and **14** are able to perform the RCM of sterically demanding dienes to form tri- and tetrasubstituted olefins.[71,73] In addition, catalyst **14** produced the first example of CM to yield a trisubstituted olefin,[75] as well as CM and RCM reactions where one partner is directly functionalized with a deactivating group, such as acrylate or siloxane (Figure 9).[76] This catalyst has also been used to extend the scope of alkene–alkyne cross metathesis to cases where the alkyne is disubstituted and contains coordinating functionality (Figure 9).[77] Remarkably, **14** remains effective at loadings as low as 0.05 mol % for RCM reactions and 0.0001 mol % (monomer:catalyst = 1 000 000) for ROMP.[73] On the basis of these promising new applications, we expect that these catalysts will become widely used.[78]

This "next generation" of catalysts is most significant because it combines the best characteristics of early and late metal centers into a single species. Until now, it had seemed that functional group tolerance was gained at the expense of activity. Catalysts **13** and **14**, however, rival the activity of early metal catalysts such as **1** *and* retain the functional group tolerance of $(PCy_3)_2Cl_2Ru{=}CHPh$ (**4**). These developments illustrate the extent to which it is possible to tune a metal center by modifying the ligand environment.

Although the exact mechanism of these powerful new catalysts remains unclear, we have made a number of interesting observations. For example, **13** and **14** initiate much more slowly than the parent complex **4**,[79] and recent results indicate that this may be due to slower phosphine dissociation.[80] Other studies suggest that the bulky mesityl groups in these catalysts may contribute to high activity, in part because of interactions with the alkylidene moiety.[80] The mesityl substituents may also provide the metal center with considerable steric protection and contribute to the high thermal stability of these catalysts. Additional studies are underway to identify the origin of the differences between catalysts **13** and **14**, in which only the backbone of the *N*-heterocyclic carbene ligand is changed. Preliminary ab initio quantum mechanical calculations[81] and experimental evidence[82] indicate that both the $\sigma$-basicity and $\pi$-acidity of the ligands play a role in catalyst activity. Ongoing work in this laboratory is directed toward answering these questions.

## Current Directions and Outlook

Olefin metathesis has become a standard synthetic method because of the wide variety of applications that are now feasible and the ease with which $L_2X_2Ru{=}CHR$ catalysts can be used. Furthermore, the activity and functional group tolerance of ruthenium catalysts is now sufficiently high for olefin metathesis to begin to compete with more traditional carbon–carbon bond-forming methods, such as the Diels–Alder and Wittig reactions. There is considerable interest in further catalyst development, however, because these catalysts remain incapable of performing some of the most demanding transformations, including CM to form tetrasubstituted olefins and the ROMP of barrelenes. In addition, ruthenium catalysts are limited by incompatibility with basic functional groups, most notably nitriles and amines. We anticipate that these problems will be overcome in future developments as olefin metathesis chemistry continues to be an active area of research.

The next major challenge for olefin metathesis is the stereoselectivity of the reaction. Kinetic resolution and asymmetric RCM have been accomplished with chiral molybdenum-based catalysts,[83] and we are currently exploring the potential of chiral ruthenium-based systems.[73] The problem of olefin stereoselectivity in CM and macrocyclic RCM reactions is a more complex one, however. The stereochemical outcome is presumably governed by the conformations and relative stabilities of the substrate, intermediates, and products, but these factors are currently impossible to model. Thus far, we have been able to influence *E* or *Z* selectivity through steric[49] and electronic[76] substrate features in specific cases, but we currently lack a general solution to this problem.

Concurrent to the work described in this Account, additional members of this catalyst family have been developed in the laboratories of H. Werner, P. Dixneuf, K. Caulton, A. Noels, K. Kirchner, A. Fürstner, A. Hoveyda, and P. Hofmann, among others. A number of researchers are also working on the related topics of alkyne and imine metathesis.[84,85]

## Conclusions

During the past 40 years, there has been considerable progress in understanding the design and mechanism of olefin metathesis catalysts. Ruthenium-based catalysts, in particular, have undergone a dramatic evolution from simple salts to highly tuned alkylidene complexes. As we have attempted to show, a number of ideas and discoveries were instrumental in this process. High activity and stability, as well as broad functional group tolerance, have been achieved through the careful study of structure–activity relationships, and it is in this sense that the development of these catalysts has been an organometallic success story. As work toward catalysts with specifically tailored properties continues, we look forward to exciting future developments.

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